A Method of Determining the Dose of Digoxin for Heart Failure in the Modern Era

Jerry L. Bauman, PharmD; Robert J. DiDomenico, PharmD; Marlos Viana, PhD; Melissa Fitch, PharmD

Background: The therapeutic range for digoxin in heart failure has recently changed to become lower and narrower, and the new range is associated with improved mortality. However, dosing methods have not been modified to reflect this change. In this study, we sought to develop a new method to determine the initial dose of digoxin in patients with heart failure.

Methods: Over a 6-month period, medical records were screened and reviewed for hospitalized adult patients who had a steady state digoxin concentration. A multiple linear regression was estimated relating digoxin concentration, digoxin dose, creatinine clearance, and ideal body weight to generate an equation relating the dose of digoxin with these variables and a specific target digoxin concentration of 0.7 ng/mL (0.9 nmol/L). This new method was then compared with 2 existing methods.

Results: Included in the study were 54 patients (mean [SD] age, 68 [15] years, with a mean (SD) creatinine clearance of 50 (25) mL/min (0.8 [0.4] mL/s) and mean (SD) ideal body weight of 62 (11) kg. Our proposed method and the Jusko and Koup method were more accurate than the Jelliffe method in predicting digoxin concentration. Root mean square errors were as follows: for the Jelliffe method (using ideal body weight), 0.810; for the Koup and Jusko method (with heart failure), 0.401; our proposed method, 0.375. The proposed method was then used to create a dosing nomogram.

Conclusions: Because the new therapeutic window of digoxin is associated with improved outcomes, more intensive dosage refinement should be considered. To this end, we offer new dosing recommendations and a nomogram for determining the initial dose of digoxin in patients with heart failure.

Arch Intern Med. 2006;166:2539-2545

Digoxin is recommended as adjunctive therapy to angiotensin antagonists, β blockers, and diuretics in select patients with symptomatic heart failure.1,2 Despite its long history as an agent to treat heart failure, only recently has its effectiveness been linked to neurohumoral modulation in addition to positive inotropy through inhibition of sodium-potassium adenosine triphosphate. These neurohumoral actions are evident at low digoxin concentrations; further decreases in norepinephrine concentrations are not observed as the concentration of digoxin increases, that is, from 0.7 to 1.2 ng/mL (0.9-1.5 nmol/L).3 Consistent with these observations are the post hoc findings4,5 from the Digitalis Investigation Group. In the analysis of both men and women receiving digoxin for systolic heart failure,4 those with digoxin concentrations of 0.5 to 0.8 ng/mL (0.6-1.0 nmol/L) had a 6.3% lower all-cause mortality and a 5.9% lower hospitalization rate compared with patients receiving placebo. Patients with serum concentrations greater than 1.2 ng/mL (1.5 nmol/L) had an 11.8% higher mortality and also higher rates of hospitalization and digoxin toxicity than those treated with placebo. The post hoc analysis of women in the Digitalis Investigation Group trial5 yielded similar findings. These results are consistent with other retrospective analyses of large multicenter clinical trials studying the effects of digoxin patients with left ventricular dysfunction.6 In all, despite the lack of controlled prospective trials, the most recently recommended therapeutic range for digoxin when used in symptomatic heart failure is now 0.5 to 0.9 ng/mL (0.6-1.2 nmol/L)5 or less than 1.0 ng/mL (<1.3 nmol/L).2 This range is narrower and lower than the older window of 0.8 to 2.0 ng/mL (1.0-2.6 nmol/L), which was originally defined on the basis of the risk of digoxin toxicity not effectiveness.7,8

Historically, 2 methods have been used to estimate the initial dose of
have been associated with improved mortality.3-5 There-
more narrow and concentrations within this new range
goxin and closely monitoring serum digoxin concentra-
vigilance in more precisely determining the dose of di-
drug-drug interactions (eg, amiodarone, quinidine, verapamil, or macrolide antibiot-
cs), (2) documentation in the patient’s record of a history of poor medication adherence, or (3) the presence of end-stage renal dysfunction requiring dialysis or of unstable renal func-
tion (ie, acute renal failure). Patient inclusion required the unan-
mity of 3 investigators. In patients with multiple digoxin concen-
trations, only a single digoxin level that best represen-
ted steady state conditions (ie, the last trough concentra-
tion determined during hospitalization) was used in the
analysis. During the study period there were no institutional
guidelines with regard to digoxin dosing or target digoxin concen-
trations in patients with heart failure, inasmuch the
method of choosing a digoxin dose (and the resultant digoxin concentra-
tion) for an individual patient reflected the clinical
judgment of the patient’s physician. Digoxin plasma concen-
trations were measured by a turbidimetric inhibition immu-
noassay method using digoxin-specific antibodies (Synchron LX; Beckman Coulter, Fullerton, Calif.). The lower limit of
detection for this assay is 0.2 ng/mL (0.3 nmol/L), and the
within-run variation is ±0.1 ng/mL (±0.1 nmol/L). Spironolac-
tone does not interfere with the determination of digoxin con-
centration by this method; patients receiving concurrent
therapy with this agent were therefore not excluded from the
analysis.

**DETERMINATION
OF THE DOSING ALGORITHM**

The linear regression relating the patient’s digoxin concentra-
tion to the steady state maintenance dose of digoxin, the cre-
tinine clearance (calculated from serum creatinine; see the
next subsection), and the patient’s ideal body weight (IBW)
calculated according to height; see the next subsection) was
estimated from the observed data. These variables were chosen
because they have been historically demonstrated to be the
primary variables in determining the concentration of
digoxin in the plasma for a given dose. The estimated equation
served the purpose of relating the dose of digoxin as a linear
function of creatinine clearance and body weight for a specific
digoxin target concentration (ie, 0.7 ng/mL [0.9 nmol/L]). To
calculate a dosing nomogram, the lines of constant
digoxin maintenance dose as a function of creatinine clear-
ance and IBW were then derived from the linear relationships
among the dose of digoxin, estimated creatinine clearance, and
IBW.

**COMPARISON WITH
OTHER METHODS**

The dosing algorithm derived from the data set of steady state
digoxin concentrations and patient characteristics was com-
pared with 2 frequently recommended methods: that of Jel-
liffe and that of Koup and Jusko. For the Jelliffe method,14 the
predicted, or expected, digoxin plasma concentration (Cp) in
nanograms per milliliter was defined for each patient by

\[
C_p = -0.416 + (0.185 \times \text{TBS}),
\]

where

\[
\text{TBS} = \frac{\text{Dose}_{\text{ss}}}{(14 + (C_l/5)/100)} \times \text{BW}
\]

is the total body stores of digoxin, \text{Dose}_{\text{ss}} is the maintenance
dose of digoxin at steady state, \text{C}_l is the creatinine clearance
estimated from serum creatinine by the method of Cockcroft
gand Gault,15 and BW is the patient’s body weight (both IBW
estimated from height by the method of Devine16 and total body
weight were used separately to estimate different values for ex-
pected digoxin concentrations).

**METHODS**

**PATIENT SELECTION**

The laboratory records of hospitalized adult patients who had a
digoxin concentration determined over a 6-month period
were used to screen for suitable patients. This screening
procedure yielded 117 potentially eligible patients. The medical
records of these patients were then reviewed for the following
entry criteria: patients had to be older than 18 years with a
presumed steady state digoxin concentration (ie, a concentra-
tion determined in the postdistributive state [at least 6 hours
after oral digoxin administration]) when receiving a stable
dose of digoxin for a suitable time period to reach steady
state. In those patients with normal renal function (estimated
creatinine clearance, >90 mL/min [>1.5 mL/s]), the patient
needed to be receiving the same dosage of digoxin for at least
1 week and for those with reduced renal function (estimated
creatinine clearance, <90 mL/min [<1.5 mL/s]), the dose of
digoxin needed to remain unchanged for at least 1 month.
Patients were excluded from the analysis for the following
reasons: (1) the presence of significant drug-drug interactions
(eg, amiodarone, quinidine, verapamil, or macrolide antibiot-
cs), (2) documentation in the patient’s record of a history of

**Table 1. Estimated RMS Errors and Corresponding 95% CIs**

<table>
<thead>
<tr>
<th>Source and Method</th>
<th>RMS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jelliffe6-10</td>
<td>0.810 (0.614-0.944)</td>
</tr>
<tr>
<td>Ideal body weight</td>
<td>0.758 (0.557-0.895)</td>
</tr>
<tr>
<td>Total body weight</td>
<td></td>
</tr>
<tr>
<td>Koup and Jusko</td>
<td>0.460 (0.298-0.563)</td>
</tr>
<tr>
<td>Proposed method</td>
<td>0.375 (0.223-0.480)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RMS, root mean square error.
For the Koup and Jusko method,

\[ C_{pe} = \frac{F \times \text{Dose} \times 1000}{\text{Cl}_{\text{dig}} \times \tau}, \]

where \( F \) is the bioavailability of digoxin tablets (0.75), \( \tau \) is the dosing interval (once daily as 1440 min/d);

\[ \text{Cl}_{\text{dig}} = (1.303 \times \text{Cl}_{\text{cr}}) + \text{Cl}_{\text{nr}} \]

is the clearance of digoxin, and \( \text{Cl}_{\text{nr}} \) is the nonrenal clearance of digoxin, equal to 41 mL/min (0.7 mL/s) in patients with heart failure and 20 mL/min (0.3 mL/s) in patients without heart failure. Both of these values for nonrenal clearance were used separately to estimate different values for expected digoxin concentration.

The comparisons between the expected \((C_{pe})\) and observed \((C_{po})\) digoxin concentrations were estimated in terms of the root mean square error (RMS) as follows:

\[ \text{RMS} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (C_{po} - C_{pe})^2}. \]

Invariant plots relating the average, \((C_{po} + C_{pe})/2\), of observed and expected digoxin concentrations with their half-difference, \((C_{po} - C_{pe})/2\), were constructed to complement the RMS as a measure of accuracy. These 2 summaries of the data are complementary in that they are derived from and consistent with the same principle of data reduction. The RMS summarizes the data as 2 n-dimensional vectors, and the invariant plots jointly describe the n (observed and predicted) data points in 2 permutation invariant axes. These 2 summaries here serve the purpose of comparing our method, the Jelliffe method, and the Koup and Jusko method for determining the dose of digoxin. In addition, the variance of the expected digoxin concentration as a function of the dose of digoxin, the creatinine clearance, and the IBW was estimated from the present data.

### RESULTS

**PATIENTS**

From the original 117 patients, 63 were excluded from the analysis: in 39 the investigators could not be confident that the digoxin concentrations were determined at steady state, in 10 there was a drug interaction (all to amiodarone), in 6 the patient medical records were unavailable, 6 were receiving dialysis, 1 had acute renal failure, and 1 was only 7 months of age. The remaining 54 patients had digoxin concentrations that met the criteria for inclusion. Of these 54, 30 were men and 24 were women (mean [SD] age, 68 [15] years). Forty-six (85%) had a clinical diagnosis of heart failure. Of the 54 patients, 6 (11%) were receiving 0.125 mg of digoxin every other day; 36 (67%), 0.125 mg once daily; 11 (20%), 0.25 mg once daily; and 1 (2%), 0.375 mg once daily (all as digoxin tablets). In these patients, steady state digoxin concentrations used for the analysis ranged from 0.4 to 2.4 (mean [SD], 0.9 [0.4] ng/mL) (1.2 [0.5] nmol/L), and creatinine clearance ranged from 8 to 132 mL/min (0.1-2.2 mL/s). The mean (SD) values of the daily dose of digoxin, the estimated creatinine clearance, and estimated IBW were, respectively, 0.132 (0.037) mg, 49.9 (25.0) mL/min (0.8 [0.4] mL/s), and 61.8 (11.4) kg. The jointly estimated covariance (based on 51 complete joint observations) between dose and clearance, dose and IBW, and clearance and IBW were, respectively, 5.772, 2.428, and 117.436.

### DOSING EQUATION AND COMPARISON WITH EXISTING METHODS

The estimation of the linear regression required a complete set of variables for each patient. In 3 patients, 1 variable (ie, height to estimate IBW was unavailable) could not be gleaned from the patient’s medical records, leaving a complete set of 51 observations. The estimated linear regression based on this set of 51 observations relating the patient’s observed steady state digoxin concentration to the maintenance dose of digoxin (dose), the creatinine clearance (\( \text{Cl}_{\text{cr}} \)), and the IBW was

\[
C_{pe} = 1.345 + (0.287 \times \text{Dose}) - (0.007 \times \text{Cl}_{\text{cr}}) - (0.011 \times \text{IBW}).
\]

The analysis of variance F-ratio statistic for the overall linear fit was 5.687 \( (P = .002) \). The error variance estimate was \( s^2 = 0.151 \). Given a digoxin target concentration of 0.7 ng/mL (0.9 nmol/L), the resulting dose determination is estimated by

\[
\text{Dose} = -2.247 + (0.0244 \times \text{Cl}_{\text{cr}}) + (0.0383 \times \text{IBW}),
\]

where the dose of digoxin is coded as \( 1 = 0.0625 \) mg/d (or 0.125 mg every other day), \( 2 = 0.125 \) mg/d, and \( 3 = 0.25 \) mg/d.

The estimated standard deviation for the predicted concentration at the mean values (dose = 0.132 mg, IBW = 61.76 kg, and clearance = 50.7 mL/min [0.8 mL/s]) was 0.089. The estimated RMS errors and corresponding approximate large-sample 95% confidence intervals for the RMS estimates are shown in Table 1. The confidence intervals clearly indicate the superiority (in RMS terms) of the Koup and Jusko method and our proposed method relative to Jelliffe method. There is no statistical distinction between the method proposed here and the Koup and Jusko method based on these confidence intervals. Because the (square) bias is one of the components of the RMS – accuracy, we evaluated the paired mean differences \((C_{pe} - C_{po})\) of digoxin concentrations (Table 2).

**Table 2. Paired Mean Differences Between Expected and Observed (C_{po} − C_{pe}) Digoxin Plasma Concentrations**

<table>
<thead>
<tr>
<th>Source and Method</th>
<th>Mean Difference (SD)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jelliffe et al</td>
<td>-0.526 (0.604)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total body weight</td>
<td>-0.211 (0.722)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Koup and Jusko</td>
<td>0.221 (0.398)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No heart failure</td>
<td>0.008 (0.397)</td>
<td>.89</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.039 (0.377)</td>
<td>.47</td>
</tr>
<tr>
<td>Proposed method</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: \( C_{po} \), observed plasma concentration; \( C_{pe} \), expected plasma concentration.

©2006 American Medical Association. All rights reserved.

(REPRINTED WITH CORRECTIONS)

Downloaded From: http://archinte.jamanetwork.com/pdfaccess.ashx?url=/data/journals/intemed/20250/ on 06/16/2017
**Figure 1.** Invariant plots relating observed and predicted serum digoxin concentrations. Each of the invariant plots shown here plots the mean digoxin plasma concentration between observed (Cpo) and expected (Cpe) on the x-axis and the difference between observed and expected (divided by 2) on the y-axis. Invariant plots using the Jelliffe method are depicted in A (using ideal body weight) and B (using total body weight). Invariant plots using the Koup and Jusko (Koup et al11 and Jusko et al12) dosing method are depicted in C (using nonrenal clearance values for digoxin in the absence of heart failure) and D (using nonrenal clearance values for digoxin in the presence of heart failure). E, The invariant plots using the proposed digoxin dosing nomogram described in the text and depicted in Figure 2. RMS denotes root mean square error.
Complementing the RMS analysis, the invariant plots for all 5 methods are shown in Figure 1. Note that these plots add the information of whether the differences between observed and predicted concentrations vary with the magnitude of the mean responses. The invariant plot for 2 coincident data points would reduce to a single point over the horizontal line at zero. Points clustering tightly around that line correspond to a smaller RMS. We observed that both the proposed method and the Koup and Jusko method are comparable in those 2 aspects and show deviations from zero that are more uniform (in the mean value axis) relative to the Jelliffe method.

In addition, all methods of dosing showed statistically significant (all $P<.01$) correlations between expected and observed digitoxin concentrations: for the Jelliffe method using IBW ($r=0.484$), for the Jelliffe method using total body weight ($r=0.379$), for the Koup and Jusko method with heart failure ($r=0.494$), and for the Koup and Jusko method without heart failure ($r=0.441$). As could be expected, using IBW for the Jelliffe method and heart failure clearance values for the Koup and Jusko method resulted in somewhat better correlations between expected and observed digitoxin concentrations.

**COMMENT**

Our intention in this study was to create a practical way of determining the proper dosage of digitoxin when given for patients with systolic heart failure. This was done given new information that implied improved mortality with digitoxin concentrations of 0.5 to 0.9 ng/mL (0.6-1.2 nmol/L), a range narrower and lower than the range historically used (0.8-2.0 ng/mL [1.0-2.6 nmol/L]). Although the Jelliffe method was used in the Digitalis Investigation Group trial, our sense is that most clinicians have abandoned previously published methods to determine the dosage of digitoxin, perhaps because they are too cumbersome. Therefore we constructed and herein offer a nomogram wherein only estimated creatinine clearance and IBW or height are necessary to pick an initial dose of digitoxin designed to achieve a steady state concentration of 0.7 ng/mL (0.9 nmol/L).

**CREATION OF A DOSING NOMOGRAM**

From our data set and the resulting regression equation, a simple nomogram was constructed for use by clinicians in determining the initial dose of digitoxin in heart failure (target concentration, 0.7 ng/mL [0.9 nmol/L]). This nomogram is shown in Figure 2. A given patient’s recommended digitoxin dose can be estimated by plotting their creatinine clearance (x-axis) by either their IBW (y-axis) or their height (z-axis), depending on patient sex. In the 0.25-mg daily area of the nomogram, one may also consider a digitoxin maintenance dose of 0.125 mg alternating with 0.25 mg every other day (average daily dose of 0.1875 mg/day) as represented by the gradual shading of this area.
By using the proposed nomogram shown in Figure 2, most patients will require daily digoxin doses of either 0.125 mg or 0.0625 mg (0.125 mg every other day), which is lower than those recommended by existing dosing methods. In most of the 0.25-mg zone of the nomogram (particularly the lower portion), the clinician could rationally decide to begin with alternating daily doses of 0.125 and 0.25 mg of digoxin (as shown by the gradual shading in this area). However, to many this is a confusing regimen that could lead to dosing errors and possibly digoxin toxicity.21

After the nomogram was constructed, we compared the prescribed digoxin dose with that recommended by our dosing nomogram and, in turn, analyzed the resultant serum digoxin concentrations. Of the 54 patients, 33 (61%) had digoxin concentrations of 0.5 to 0.9 ng/mL (0.6-1.2 nmol/L) in the data set and similarly, 33 (65%) of 51 patients would have had concentrations within this range using our nomogram. However, of the 54 patients in the data set, 19 (35%) had digoxin concentrations greater than 1.0 ng/mL (>1.3 mmol/L) whereas only 11 (22%) of 51 would have had concentrations greater than 1.0 ng/mL (>1.3 mmol/L) if dosed according to the proposed method. Alternatively, recent guidelines19 suggest the digoxin concentration should be less than 1.0 ng/mL (<1.3 mmol/L) in patients with heart failure. Using this as a goal, of the 54 patients in the data set, 33 (61%) had digoxin concentrations less than 1.0 ng/mL (<1.3 mmol/L) whereas with the doses recommended by the proposed nomogram, it was estimated that 40 (78%) of 51 patients would have had digoxin concentrations less than 1.0 ng/mL (<1.3 mmol/L). These data suggest a tendency for the dose recommended by our proposed nomogram to less frequently result in undesirable higher concentrations (>1.0 ng/mL [>1.3 mmol/L]) compared with those in our data set, perhaps reflecting “usual medical care.” However, comparisons of this type would be better served by a prospective randomized trial with a larger sample size.

Our method was more precise (using RMS) in predicting the patient’s digoxin concentration than the Jelliffe method and somewhat more precise (although not statistically distinct) than the Koup and Jusko method. Although the Jelliffe method was originally designed to result in a concentration of about 1.4 ng/mL (1.8 nmol/L), both of the older methods can be adapted to estimate a dose of digoxin that would result in an expected digoxin concentration of 0.7 ng/mL (0.9 nmol/L). The Koup and Jusko method particularly when using heart failure digoxin clearance values was more precise than the Jelliffe method. This finding is similar to Koup and Jusko’s original observations in which their method performed better than a method similar to Jelliffe’s, which gives us a degree of confidence in our data set (despite the retrospective nature of the data collection). Using the Koup and Jusko method (for heart failure patients) and a target digoxin concentration of 0.7 ng/mL (0.9 nmol/L), one can develop dosing suggestions based on the patient’s renal function. They are as follows, based on creatinine clearance (according to Cockcroft and Gault22) values:

- Less than 30 mL/min (≤0.5 mL/s): start at 0.125 mg every other day
- 30 to 80 mL/min (0.5-1.3 mL/s): start at 0.125 mg every day
- 80 to 120 mL/min (1.3-2.0 mL/s): start at 0.25 mg alternating with 0.125 mg every day
- Greater than 120 mL/min (≥2.0 mL/s): start at 0.25 mg every day

The median dose of digoxin in the Digitalis Investigation Group trial was 0.25 mg/d.11 Because of the more recent emphasis on using lower maintenance doses of digoxin, one could consider empirically an initial treatment of 0.125 mg/d of digoxin in nearly all patients with heart failure.2 However, according to our results, most patients (depending on height or IBW) with even moderate (stage 3) renal insufficiency (creatinine clearance, <60 mL/min [≤1.0 mL/s]) should receive 0.125 mg of digoxin every other day. In the Digitalis Investigation Group trial,22 46% of patients enrolled had glomerular filtration rates of less than 60 mL/min per 1.73 m². Hence, given the importance of maintaining the digoxin concentration within the narrow window associated with improved mortality, we propose using our dosing guidelines to determine the initial dose of digoxin. Subsequently, the digoxin concentration should be monitored and the dose of digoxin adjusted to ensure that the chronic steady state dose results in trough concentrations of 0.5 to 0.9 ng/mL (0.6-1.2 nmol/L).

One additional point in this regard could be made. Digoxin tablets are the most commonly prescribed dosage form but are available only in 0.125- and 0.25-mg strengths. Our results and the need to perhaps be more precise in tailoring chronic dosing regimens to obtain therapeutic concentrations should prompt the availability of new strengths, such as 0.0625- and 0.1875-mg tablets.

Accepted for Publication: May 31, 2006.
Correspondence: Jerry L. Bauman, PharmD, University of Illinois at Chicago, M/C 886, 833 Wood St, Chicago, IL 60612 (jbauman@uic.edu).

Author Contributions: Study concept and design: Bauman, DiDomenico, Viana, and Fitch. Acquisition of data: Bauman and Fitch. Analysis and interpretation of data: Bauman, DiDomenico, Viana, and Fitch. Drafting of the manuscript: Bauman, DiDomenico, and Viana. Critical revision of the manuscript for important intellectual content: Bauman, DiDomenico, Viana, and Fitch. Statistical analysis: Viana. Administrative, technical, and material support: Bauman and DiDomenico. Study supervision: Bauman and DiDomenico.

Financial Disclosure: None reported.

REFERENCES


©2006 American Medical Association. All rights reserved.
(REPRINTED WITH CORRECTIONS)

Downloaded From: http://archinte.jamanetwork.com/pdfaccess.ashx?url=/data/journals/intemed/20250/ on 06/16/2017
Correction

Error in Dose Equation. In the Original Investigation by Bauman et al titled “A Method of Determining the Dose of Digoxin for Heart Failure in the Modern Era” published in the December 11/25, 2006, issue of the Archives (2006;166:2539-2545), there is an error in the second equation in the “Dosing Equation and Comparison With Existing Methods” subsection on page 2541. It should read as follows:

Dose = –2.247 + (0.0244 × Clcr) + (0.0383 × IBW).